Search Results -

Terms	Documents
(water or aqueous)[ab,ti,clm] and (polymer or copolymer or resin or binder or rubber or elastomer)[ab,ti,clm] and (filler or pigment) and (polyisocyanate or isocyanate) and (dispersing or dispersant or emulsifier or emulsifying or (surface adj active))[ab,ti,clm] and (latex or emulsion)[ab,ti,clm] and (antifoam or (anti adj foam)) and (crosslink or crosslinked or crosslinker or crosslinking)	16

Database: US Patents Full-Text Database
US Pre-Grant Publication Full-Text Database
JPO Abstracts Database
EPO Abstracts Database
Derwent World Patents Index
IBM Technical Disclosure Bulletins

Search: L5

Refine Search

Recall Text | Clear

Search History

DATE: Thursday, May 23, 2002 Printable Copy Create Case

appropriate morphology (i.e. a perforated configuration) and density. Among other methods, perforated microstructures compatible with the instant invention may be formed by techniques including lyophilization, spray drying, multiple emulsion, micronization, or crystallization. It will further be appreciated that, the basic concepts of many of these techniques are well known in the prior art and would not, in view of the teachings herein, require undue experimentation to adapt them so as to provide the desired perforated microstructures.

While several procedures are generally compatible with the present invention, particularly preferred embodiments typically comprise perforated microstructures formed by spray drying. As is well known, spray drying is a one-step process that converts a liquid feed to a dried particulate form. With respect to pharmaceutical applications, it will be appreciated that, spray drying has been used to provide powdered material for various administrative routes including inhalation. See, for example, M. Sacchetti and M. M. Van Oort in: Inhalation Aerosols: Physical and Biological Basis for Therapy, A. J. Hickey, ed. Marcel Dekkar, New York, 1996, which is incorporated herein by reference.

In general, spray drying consists of bringing together a highly dispersed liquid, and a sufficient volume of hot air to produce evaporation and drying of the liquid droplets. The preparation to be spray dried or feed (or feed stock) can be any solution, course suspension, slurry, colloidal dispersion, or paste that may be atomized using the selected spray drying apparatus. Typically, the feed is sprayed into a current of warm filtered air that evaporates the solvent and conveys the dried product to a collector. The spent air is then exhausted with the solvent. Those skilled in the art will appreciate that, several different types of apparatus may be used to provide the desired product. For example, commercial spray dryers manufactured by Buchi Ltd. or Niro Corp. will effectively produce particles of desired size. It will further be appreciated that, these spray dryers, and specifically their atomizers, may be modified or customized for specialized applications, i.e. the simultaneous spraying of two solutions using a double nozzle technique. More specifically, a water-in-oil emulsion can be atomized from one nozzle and a solution containing an anti-adherent such as mannitol can be co-atomized from a second nozzle. In other cases, it may be desirable to push the feed solution though a custom designed nozzle using a high pressure liquid chromatography (HPLC) pump. Provided that microstructures comprising the correct morphology and/or composition are produced, the choice of apparatus is not critical and would be apparent to the skilled artisan in view of the teachings herein.

While the resulting spray-dried powdered particles typically are approximately spherical in shape, nearly uniform in size and frequently are hollow, there may be some degree of irregularity in shape depending upon the incorporated medicament and the spray drying conditions. In many instances the dispersion stability of spray-dried microspheres appears to be more effective if an inflating agent (or blowing agent) is used in their production. Particularly preferred embodiments may comprise an emulsion with the inflating agent as the disperse or continuous phase (the other phase being aqueous in nature). The inflating agent is preferably dispersed with a surfactant solution, using, for instance, a commercially available microfluidizer at a pressure of about 5000 to 15,000 psi. This process forms an emulsion, preferably stabilized by an incorporated surfactant, typically comprising submicron droplets of water immiscible blowing agent dispersed in an aqueous continuous phase. The formation of such dispersions using this and other techniques are common and well known to those in the art. The blowing agent is preferably a fluorinated compound (e.g. perfluorohexane, perfluorooctyl bromide, perfluorodecalin, perfluorobutyl ethane) which vaporizes during the spray-drying process, leaving behind generally hollow, porous aerodynamically light microspheres. As will be discussed in more detail below, other suitable blowing agents include chloroform, Freons, and hydrocarbons. Nitrogen gas and carbon dioxide are also contemplated as a suitable blowing agent.

Although the perforated microstructures are preferably formed using a blowing agent as described above, it will be appreciated that, in some instances, no blowing agent is required and an aqueous dispersion of the medicament and surfactant(s) are spray dried directly. In such cases, the formulation may be amenable to process conditions (e.g., elevated temperatures) that generally lead to the formation of hollow, relatively porous microparticles. Moreover, the medicament may possess special physicochemical properties (e.g., high crystallinity, elevated melting temperature, surface activity, etc.) that make it particularly suitable for use in such techniques.

When a blowing agent is employed, the degree of porosity of the perforated microstructure appears to depend, at least in part, on the nature of the blowing agent, its concentration in the feed stock (i.e. as an emulsion), and the spray drying conditions. With respect to controlling porosity, it has surprisingly been found that the use of compounds, heretofore unappreciated as blowing agents, may provide perforated microstructures having particularly desirable characteristics. More particularly, in this novel and unexpected aspect of the present invention it has been found that the use of fluorinated compounds having relatively high boiling points (i.e. greater than about 60° C.) may be used to produce particulates that are especially suitable for inhalation therapies. In this regard, it is possible to use fluorinated blowing agents having boiling points of greater than about 70° C., 80° C., 90° C. or even 95° C. Particularly preferred blowing agents have boiling points greater than the boiling point of water, i.e. greater than 100° C. (e.g. perflubron, perfluorodecalin). In addition, blowing agents with relatively low water solubility ($<^{-6}$ M) are preferred since they enable the production of stable emulsion dispersions with mean weighted particle diameters less than 0.3 μm. As indicated above, these blowing agents will preferably be incorporated in an emulsified feed stock prior to spray drying. For the purposes of the present invention this feed stock will also preferably comprise one or more bioactive agents, one or more surfactants, or one or more excipients. Of course, combinations of the aforementioned components are also within the scope of the invention

While not limiting the invention in any way it is hypothesized that, as the aqueous feed component evaporates during spray drying it leaves a thin crust at the surface of the particle. The resulting particle wall or crust formed during the initial moments of spray drying appears to trap any high boiling blowing agents as hundreds of emulsion droplets (ca. 200–300 nm). As the drying process continues, the pressure inside the particulate increases thereby vaporizing at least part of the incorporated blowing agent and forcing it through the relatively thin crust. This venting or outgassing apparently leads to the formation of pores or other defects in the crust. At the same time, remaining particulate components (possibly including some blowing agent) migrate from the interior to the surface as the particle solidifies. This migration apparently slows during the drying process as a result of

Set Name side by side	Query	Hit Count	Set Name result set
	DB=USPT; PLUR=YES; OP=OR		
L5	(water or aqueous)[ab,ti,clm] and (polymer or copolymer or resin or binder or rubber or elastomer)[ab,ti,clm] and (filler or pigment) and (polyisocyanate or isocyanate) and (dispersing or dispersant or emulsifier or emulsifying or (surface adj active))[ab,ti,clm] and (latex or emulsion)[ab,ti,clm] and (antifoam or (anti adj foam)) and (crosslink or crosslinked or crosslinker or crosslinking)	16	L5
L4	(water or aqueous)[ab,ti,clm] and (polymer or copolymer or resin or binder or rubber or elastomer)[ab,ti,clm] and (filler or pigment) and (polyisocyanate or isocyanate) and (dispersing or dispersant or emulsifier or emulsifying or (surface adj active)) and (latex or emulsion)[ab,ti,clm] and (antifoam or (anti adj foam)) and (crosslink or crosslinked or crosslinker or crosslinking)	59	L4
L3	(water or aqueous)[ab,ti,clm] and (polymer or copolymer or resin or binder or rubber or elastomer)[ab,ti,clm] and (filler or pigment) and (polyisocyanate or isocyanate) and (dispersing or dispersant or emulsifier or emulsifying or (surface adj active)) and (latex or emulsion) and (antifoam or (anti adj foam)) and (crosslink or crosslinked or crosslinker or crosslinking)	130	L3
L2	(water or aqueous)[ab,ti,clm] and (polymer or copolymer or resin or binder or rubber or elastomer) and (filler or pigment) and (polyisocyanate or isocyanate) and (dispersing or dispersant or emulsifier or emulsifying or (surface adj active)) and (latex or emulsion) and (antifoam or (anti adj foam)) and (crosslink or crosslinked or crosslinker or crosslinking)	146	L2
L1	(water or aqueous) and (polymer or copolymer or resin or binder or rubber or elastomer) and (filler or pigment) and (polyisocyanate or isocyanate) and (dispersing or dispersant or emulsifier or emulsifying or (surface adj active)) and (latex or emulsion) and (antifoam or (anti adj foam)) and (crosslink or crosslinked or crosslinker or crosslinking)	198	L1

END OF SEARCH HISTORY

accordance with the invention include anti-allergics, peptides and proteins, bronchodilators and anti-inflammatory steroids for use in the treatment of respiratory disorders such as asthma by inhalation therapy.

It will be appreciated that, the perforated microstructures of the present invention may exclusively comprise one or more bioactive agents (i.e. 100% w/w). However, in selected embodiments the perforated microstructures may incorporate much less bioactive agent depending on the activity thereof. Accordingly, for highly active materials the perforated microstructures may incorporate as little as 0.001% by weight although a concentration of greater than about 0.1% w/w is preferred. Other embodiments of the invention may comprise greater than about 5%, 10%, 15%, 20%, 25%, 30% or even 40% w/w bioactive agent. Still more preferably, the perforated microstructures may comprise greater than about 50%, 60%, 70%, 75%, 80% or even 90% w/w bioactive agent. In particularly preferred embodiments, the final stabilized respiratory dispersion desirably contains from about 40%–60% w/w, more preferably 50%–70% w/w, and even more preferably 60%–90% w/w of bioactive agent relative to the weight of the microparticulate matrix. The precise amount of bioactive agent incorporated in the stabilized dispersions of the present invention is dependent upon the agent of choice, the required dose, and the form of the drug actually used for incorporation. Those skilled in the art will appreciate that, such determinations may be made by using well-known pharmacological techniques in combination with the teachings of the present invention.

Accordingly, bioactive agents that may be administered in the form of aerosolized medicaments in conjunction with the teachings herein include any drug that may be presented in a form which is relatively insoluble in the selected propellant and subject to pulmonary uptake in physiologically effective amounts. Compatible bioactive agents comprise hydrophilic and lipophilic respiratory agents, bronchodilators, antibiotics, antivirals, pulmonary lung surfactants, anti-inflammatories, steroids, antihistaminics, leukotriene inhibitors or antagonists, anticholinergics, antineoplastics, anesthetics, enzymes, cardiovascular agents, genetic material including DNA and RNA, viral vectors, immunoactive agents, imaging agents, vaccines, immunosuppressive agents, peptides, proteins and combinations thereof. Particularly preferred bioactive agents for administration using aerosolized medicaments in accordance with the present invention include mast cell inhibitors (anti-allergics), bronchodilators, and anti-inflammatory steroids for use in the treatment of respiratory disorders such as asthma by inhalation therapy, for example cromoglycate (e.g. the sodium salt), and albuterol (e.g. the sulfate salt). For systemic delivery (e.g. delivery of the bioactive agent to the systemic circulation for the treatment of autoimmune diseases such as diabetes or multiple sclerosis), peptides and proteins are particularly preferred.

Exemplary medicaments or bioactive agents may be selected from, for example, analgesics, e.g. codeine, dihydromorphine, ergotamine, fentanyl, or morphine; anginal preparations, e.g. diltiazem; mast cell inhibitors, e.g. cromolyn sodium; antiinfectives, e.g. cephalosporins, macrolides, quinolines, penicillins, streptomycin, sulphonamides, tetracyclines and pentamidine; antihistamines, e.g. methapyrilene; anti-inflammatories, e.g. fluticasone propionate, beclomethasone dipropionate, flunisolide, budesonide, tripedane, cortisone, prednisone, prednisilone, dexamethasone, betamethasone, or triamcinolone acetonide; antitussives, e.g. noscapine; bronchodilators, e.g. ephedrine, adrenaline, fenoterol, formoterol, isoprenaline, metaproterenol, salbutamol, albuterol, salmeterol, terbutaline; diuretics, e.g. amiloride; anticholinergics, e.g. ipatropium, atropine, or oxitropium; lung surfactants e.g. Surfaxin, Exosurf, Survanta; xanthines, e.g. aminophylline, theophylline, caffeine; therapeutic proteins and peptides, e.g. DNAse, insulin, glucagon, LHRH, nafarelin, goserelin, leuprolide, interferon, rhu IL-1 receptor, macrophage activation factors such as lymphokines and muramyl dipeptides, opioid peptides and neuropeptides such as enkaphalins, endorphins, renin inhibitors, cholecystokinins, DNAse, growth hormones, leukotriene inhibitors and the like. In addition, bioactive agents that comprise an RNA or DNA sequence, particularly those useful for gene therapy, genetic vaccination, genetic tolerization, or antisense applications, may be incorporated in the disclosed dispersions as described herein. Representative DNA plasmids include pCMVβ (available from Genzyme Corp, Framington, Mass.) and pCMV-β-gal (a CMV promotor linked to the *E. coli* Lac-Z gene, which codes for the enzyme β-galactosidase).

The selected bioactive agent(s) may comprise, be associated with, or incorporated in, the perforated microstructures in any form that provides the desired efficacy and is compatible with the chosen production techniques. As used herein, the terms "associate" or "associating" mean that the structural matrix or perforated microstructure may comprise, incorporate, adsorb, absorb, be coated with or be formed by the bioactive agent. Where appropriate, the medicaments may be used in the form of salts (e.g. alkali metal or amine salts or as acid addition salts) or as esters or as solvates (hydrates). In this regard, the form of the bioactive agents may be selected to optimize the activity and/or stability of the medicament and/or to minimize the solubility of the medicament in the suspension medium. It will further be appreciated that, the aerosolized formulations according to the invention may, if desired, contain a combination of two or more active ingredients. The agents may be provided in combination in a single species of perforated microstructure or individually in separate species of perforated microstructures that are combined in the suspension medium. For example, two or more bioactive agents may be incorporated in a single feed stock preparation and spray dried to provide a single microstructure species comprising a plurality of medicaments. Conversely, the individual medicaments could be added to separate stocks and spray dried separately to provide a plurality of microstructure species with different compositions. These individual species could be added to the propellant medium in any desired proportion and placed in the aerosol delivery system as described below. Further, as briefly mentioned above, the perforated microstructures (with or without an associated medicament) may be combined with one or more conventionally micronized bioactive agents to provide the desired dispersion stability.

Based on the foregoing, it will be appreciated by those skilled in the art that a wide variety of bioactive agents may be incorporated in the disclosed stabilized dispersions. Accordingly, the list of preferred bioactive agents above is exemplary only and not intended to be limiting. It will also be appreciated by those skilled in the art that the proper amount of bioactive agent and the timing of the dosages may be determined for the formulations in accordance with already existing information and without undue experimentation.

As seen from the passages above, various components may be associated with, or incorporated in the perforated microstructures of the present invention. Similarly, several techniques may be used to provide particulates having the

Search Results -

Terms	Documents
L7 not l5	4

Database:
- US Patents Full-Text Database
- US Pre-Grant Publication Full-Text Database
- JPO Abstracts Database
- EPO Abstracts Database
- Derwent World Patents Index
- IBM Technical Disclosure Bulletins

Search: L8

Refine Search

Recall Text | Clear

Search History

DATE: Thursday, May 23, 2002 Printable Copy Create Case

instrumentation or by visual inspection. The time necessary for the suspended particulates to cream to ½ the volume of the suspension medium (i.e., to rise to the top half of the suspension medium), or to sediment within ½ the volume (i.e., to settle in the bottom ½ of the medium), is then noted. Suspension formulations having a creaming time greater than 1 minute are preferred and indicate suitable stability. More preferably, the stabilized dispersions comprise creaming times of greater than 1, 2, 5, 10, 15, 20 or 30 minutes. In particularly preferred embodiments, the stabilized dispersions exhibit creaming times of greater than about 1, 1.5, 2, 2.5, or 3 hours.

Substantially equivalent periods for sedimentation times are indicative of compatible dispersions.

Regardless of the ultimate composition or precise creaming time, the stabilized respiratory dispersions of the present invention preferably comprise a plurality of perforated microstructures, or microparticulates that are dispersed or suspended in the suspension medium.

In such cases, the perforated microstructures comprise a structural matrix that exhibits, defines or comprises voids, pores, defects, hollows, spaces, interstitial spaces, apertures, perforations or holes that allows the surrounding suspension medium to freely permeate, fill or pervade the microstructure. The absolute shape (as opposed to the morphology) of the perforated microstructure is generally not critical and any overall configuration that provides the desired stabilization characteristics is contemplated as being within the scope of the invention. Accordingly, preferred embodiments can comprise approximately microspherical shapes. However, collapsed, deformed or fractured particulates are also compatible. With this caveat, it will be appreciated that, particularly preferred embodiments of the invention comprise spray dried hollow, porous microspheres.

In order to maximize dispersion stability and optimize distribution upon administration, the mean geometric particle size of the perforated microstructures is preferably about 0.5–50 μm, more preferably 1–30 μm. It will be appreciated that, large particles (i.e. greater than 50 μm) should not be used as large particles may tend to aggregate, separate from the suspension and clog the valve or orifice of the container. In especially preferred embodiments, the mean geometric particle size (or diameter) of the perforated microstructures is less than 20 μm or less than 10 μm. More preferably, the mean geometric diameter is less than about 5 μm, and even more preferably, less than about 2.5 μm. In especially preferred embodiments, the perforated microstructures will comprise a powder of dry, hollow, porous microspherical shells of approximately 1 to 10 μm in diameter, with shell thicknesses of approximately 0.1 μm to approximately 0.5 μm. It is a particular advantage of the present invention that the particulate concentration of the dispersions and structural matrix components can be adjusted to optimize the delivery characteristics of the selected particle size.

As discussed throughout the instant specification, the porosity of the microstructures may play a significant part in establishing dispersion stability. In this respect, the mean porosity of the perforated microstructures may be determined through electron microscopy coupled with modern imaging techniques. More specifically, electron micrographs of representative samples of the perforated microstructures may be obtained and digitally analyzed to quantify the porosity of the preparation. Such methodology is well known in the art and may be undertaken without undue experimentation.

For the purposes of the present invention, the mean porosity (i.e. the percentage of the particle surface area that is open to the interior and/or a central void) of the perforated microstructures may range from approximately 0.5% to approximately 80%. In more preferred embodiments, the mean porosity will range from approximately 2% to approximately 40%. Based on selected production parameters, the mean porosity may be greater than approximately, 2%, 5%, 10%, 15%, 20%, 25% or 30% of the microstructure surface area. In other embodiments, the mean porosity of the microstructures may be greater than about 40%, 50%, 60%, 70% or even 80%. As to the pores themselves, they typically range in size from about 5 nm to about 400 nm, with mean pore sizes preferably in the range of from about 20 nm, to about 200 nm. In particularly preferred embodiments, the mean pore size will be in the range of from about 50 nm to about 100 nm. As may be seen in FIGS. **1A1** to **1F2**, and discussed in more detail below, it is a significant advantage of the present invention that the pore size and porosity may be closely controlled by careful selection of the incorporated components and production parameters.

Along with the geometric configuration, the perforated or porous and/or hollow design of the microstructures also plays an important role in the resulting aerosol properties upon activation of the MDI. In this respect, the perforated structure and relatively high surface area of the dispersed microparticles enables them to be carried along in the flow of gases during inhalation with greater ease for longer distances than non-perforated particles of comparable size. Because of their high porosity, the density of the particles is significantly less than 1.0 g/cm^3, typically less than 0.5 g/cm^3, more often on the order of 0.1 g/cm^3, and as low as 0.01 g/cm^3. Unlike the geometric particle size, the aerodynamic particle size, d_{aer}, of the perforated microstructures depends substantially on the particle density, ρ: $d_{aer}=d_{geo}\rho$, where d_{geo}, is the geometric diameter. For a particle density of 0.1 g/cm^3, d_{aer}, will be roughly three times smaller than d_{geo}, leading to increased particle deposition into the peripheral regions of the lung and correspondingly less deposition in the throat. In this regard, the mean aerodynamic diameter of the perforated microstructures is preferably less than about 5 μm, more preferably less than about 3 μm, and, in particularly preferred embodiments, less than about 2 μm. Such particle distributions will act to increase the deep lung deposition of the administered agent.

As will be shown subsequently in the Examples, the particle size distribution of the aerosol formulations of the present invention are measurable by conventional techniques such as, for example, cascade impaction or by time of flight analytical methods. Determination of the emitted dose in pressurized inhalations was done according to the proposed U.S. Pharmacopeia method (*Pharmacopeial Previews,* 22(1996) 3065) which is incorporated herein by reference. These and related techniques enable the "fine particle fraction" of the aerosol, which corresponds to those particulates that are likely to effectively deposited in the lung, to be calculated. As used herein the phrase "fine particle fraction" refers to the percentage of the total amount of active medicament delivered per actuation from the mouthpiece onto plates 2–7 of an 8 stage Andersen cascade impactor. Based on such measurements, the formulations of the present invention will preferably have a fine particle fraction of approximately 20% or more by weight of the perforated microstructures (w/w). More preferably, they will exhibit a fine particle fraction of from about 25% to 80% w/w, and even more preferably from about 30 to 70% w/w. In selected embodiments the present invention will preferably comprise a fine particle fraction of greater than about 30%, 40%, 50%, 60%, 70% or 80% by weight

Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT; PLUR=YES; OP=OR			
L8	L7 not l5	4	L8
L7	(water or aqueous)[ab,ti,clm] and (polymer or copolymer or resin or binder or rubber or elastomer)[ab,ti,clm] and (filler or pigment) and (polyisocyanate or isocyanate)[ab,ti,clm] and (dispersing or dispersant or emulsifier or emulsifying or (surface adj active))[ab,ti,clm] and (latex or emulsion)[ab,ti,clm] and (antifoam or (anti adj foam))	8	L7
L6	(water or aqueous)[ab,ti,clm] and (polymer or copolymer or resin or binder or rubber or elastomer)[ab,ti,clm] and (filler or pigment) and (polyisocyanate or isocyanate) and (dispersing or dispersant or emulsifier or emulsifying or (surface adj active))[ab,ti,clm] and (latex or emulsion)[ab,ti,clm] and (antifoam or (anti adj foam))	23	L6
L5	(water or aqueous)[ab,ti,clm] and (polymer or copolymer or resin or binder or rubber or elastomer)[ab,ti,clm] and (filler or pigment) and (polyisocyanate or isocyanate) and (dispersing or dispersant or emulsifier or emulsifying or (surface adj active))[ab,ti,clm] and (latex or emulsion)[ab,ti,clm] and (antifoam or (anti adj foam)) and (crosslink or crosslinked or crosslinker or crosslinking)	16	L5
L4	(water or aqueous)[ab,ti,clm] and (polymer or copolymer or resin or binder or rubber or elastomer)[ab,ti,clm] and (filler or pigment) and (polyisocyanate or isocyanate) and (dispersing or dispersant or emulsifier or emulsifying or (surface adj active)) and (latex or emulsion)[ab,ti,clm] and (antifoam or (anti adj foam)) and (crosslink or crosslinked or crosslinker or crosslinking)	59	L4
L3	(water or aqueous)[ab,ti,clm] and (polymer or copolymer or resin or binder or rubber or elastomer)[ab,ti,clm] and (filler or pigment) and (polyisocyanate or isocyanate) and (dispersing or dispersant or emulsifier or emulsifying or (surface adj active)) and (latex or emulsion) and (antifoam or (anti adj foam)) and (crosslink or crosslinked or crosslinker or crosslinking)	130	L3
L2	(water or aqueous)[ab,ti,clm] and (polymer or copolymer or resin or binder or rubber or elastomer) and (filler or pigment) and (polyisocyanate or isocyanate) and (dispersing or dispersant or emulsifier or emulsifying or (surface adj active)) and (latex or emulsion) and (antifoam or (anti adj foam)) and (crosslink or crosslinked or crosslinker or crosslinking)	146	L2
L1	(water or aqueous) and (polymer or copolymer or resin or binder or rubber or elastomer) and (filler or pigment) and (polyisocyanate or isocyanate) and (dispersing or dispersant or emulsifier or emulsifying or (surface adj active)) and (latex or emulsion) and (antifoam or (anti adj foam)) and (crosslink or crosslinked or crosslinker or crosslinking)	198	L1

w/w) of surfactant (e.g. lecithin, Span-85, oleic acid) to increase electrostatic repulsion between particles. In sharp contrast, the suspensions of the present invention are designed not to increase repulsion between particles, but rather to decrease the attractive forces between particles. The principal forces driving flocculation in nonaqueous media are van der Waals attractive forces. Van der Waals forces are quantum mechanical in origin, and can be visualized as attractions between fluctuating dipoles (i.e. induced dipole-induced dipole interactions). Dispersion forces are extremely short-range and scale as the sixth power of the distance between atoms. When two macroscopic bodies approach one another the dispersion attractions between the atoms sums up. The resulting force is of considerably longer range, and depends on the geometry of the interacting bodies.

More specifically, for two spherical particles, the magnitude of the van der Waals potential, V_A, can be approximated by:

$$V_A = \frac{-A_{eff}}{6H_0}\frac{R_1 R_2}{(R_1 + R_2)},$$

where A_{eff} is the effective Hamaker constant which accounts for the nature of the particles and the medium, H_0 is the distance between particles, and R_1 and R_2 are the radii of spherical particles 1 and 2. The effective Hamaker constant is proportional to the difference in the polarizabilities of the dispersed particles and the suspension medium: $A_{eff}=(\sqrt{A_{Sm}}-\sqrt{A_{PART}})^2$, where A_{SM} and A_{PART} are the Hamaker constants for the suspension medium and the particles, respectively. As the suspended particles and the dispersion medium become similar in nature, A_{SM} and A_{PART} become closer in magnitude, and A_{eff} and V_A become smaller. That is, by reducing the differences between the Hamaker constant associated with suspension medium and the Hamaker constant associated with the dispersed particles, the effective Hamaker constant (and corresponding van der Waals attractive forces) may be reduced.

One way to minimize the differences in the Hamaker constants is to create a "homodispersion", that is make both the continuous and dispersed phases essentially indistinguishable as discussed above. In addition to exploiting the morphology of the particles to reduce the effective Hamaker constant, the components of the structural matrix (defining the perforated microstructures) will preferably be chosen so as to exhibit a Hamaker constant relatively close to that of the selected suspension medium. In this respect, one may use the actual values of the Hamaker constants of the suspension medium and the particulate components to determine the compatibility of the dispersion ingredients and provide a good indication as to the stability of the preparation. Alternatively, one could select relatively compatible perforated microstructure components and suspension mediums using readily discernible characteristic physical values that coincide with measurable Hamaker constants.

In this respect, it has been found that the refractive index values of many compounds tend to scale with the corresponding Hamaker constant. Accordingly, easily measurable refractive index values may be used to provide a fairly good indication as to which combination of suspension medium and particle excipients will provide a dispersion having a relatively low effective Hamaker constant and associated stability. It will be appreciated that, since refractive indices of compounds are widely available or easily derived, the use of such values allows for the formation of stabilized dispersions in accordance with the present invention without undue experimentation. For the purpose of illustration only, the refractive indices of several compounds compatible with the disclosed dispersions are provided in Table I immediately below:

TABLE I

Compound	Refractive Index
HFA-134a	1.172
HFA-227	1.223
CFC-12	1.287
CFC-114	1.288
PFOB	1.305
Mannitol	1.333
Ethanol	1.361
n-octane	1.397
DMPC	1.43
Pluronic F-68	1.43
Sucrose	1.538
Hydroxyethylstarch	1.54
Sodium chloride	1.544

Consistent with the compatible dispersion components set forth above, those skilled in the art will appreciate that, the formation of dispersions wherein the components have a refractive index differential of less than about 0.5 is preferred. That is, the refractive index of the suspension medium will preferably be within about 0.5 of the refractive index associated with the perforated particles or microstructures. It will further be appreciated that, the refractive index of the suspension medium and the particles may be measured directly or approximated using the refractive indices of the major component in each respective phase. For the perforated microstructures, the major component may be determined on a weight percent basis. For the suspension medium, the major component will typically be derived on a volume percentage basis. In selected embodiments of the present invention the refractive index differential value will preferably be less than about 0.45, about 0.4, about 0.35 or even less than about 0.3. Given that lower refractive index differentials imply greater dispersion stability, particularly preferred embodiments comprise index differentials of less than about 0.28, about 0.25, about 0.2, about 0.15 or even less than about 0.1. It is submitted that a skilled artisan will be able to determine which excipients are particularly compatible without undue experimentation given the instant disclosure. The ultimate choice of preferred excipients will also be influenced by other factors, including biocompatibility, regulatory status, ease of manufacture, cost.

In contrast to prior art attempts to provide stabilized suspensions which require excipients (i.e. surfactants) that are soluble in the suspension medium, the present invention provides for stabilized dispersions, at least in part, by immobilizing the bioactive agent(s) and excipients within the structural matrix of the hollow, porous microstructures. Accordingly, preferred excipients useful in the present invention are substantially insoluble in the suspension medium. Under such conditions, even surfactants like, for example, lecithin cannot be considered to have surfactant properties in the present invention since surfactant performance requires the amphiphile to be reasonably soluble in the suspension medium. The use of insoluble excipients also reduces the potential for particle growth by Ostwald ripening.

As discussed above, the minimization of density differences between the particles and the continuous phase is largely dependent on the perforated and/or hollow nature of the microstructures, such that the suspension medium con-